Steroid withdrawal after long-term medication for immunosuppressive therapy in renal transplant patients: adrenal response and clinical implications

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Abstract: Background. Withdrawal of steroids should be attempted after organ transplantation because of their adverse cardiovascular and metabolic effects. However, immunological, haemodynamic and symptomatic complications may occur due to the suppression of endogenous corticoid hormone synthesis under exogenous steroid intake. We have examined the effect of chronic steroid medication on adrenocortical function, and of steroid withdrawal, in immunologically stable renal transplant patients. Methods. Sixty-three patients under long-term prednisone therapy (mean±SD 36±47 months) were assessed regarding basal fasting cortisol concentration and adrenocortical stimulation by the low-dose Synacten test both prior to and after stepwise prednisone withdrawal. Renal graft function (determined as the calculated glomerular filtration rate according to the Cockroft-Gault formula), mean arterial blood pressure and clinical status were evaluated concomitantly. Results. Basal fasting cortisol concentration was clearly suppressed in 14% of patients under long-term steroid medication, and adrenocortical stimulation by the low-dose Synacten test was impaired in 31% after steroid withdrawal. About a third of all patients were symptomatic with fatigue (60%), arthralgias (60%), muscular weakness (20%), loss of appetite (20%), hypotension (15%) or headaches (5%). The incidence of symptoms was much higher in patients with low basal fasting cortisol concentration prior to steroid withdrawal, and after >2 years of steroid medication. Renal graft function, determined as glomerular filtration rate, decreased only slightly overall by 5%, and was more pronounced in symptomatic vs asymptomatic patients (−7 vs −2 ml/min, respectively), as was the fall in mean arterial pressure (−10 vs −4.2 mmHg, respectively). Conclusions. Adrenal function is impaired in renal transplant patients receiving long-term steroid medication as part of their immunosuppressive regimen. This may lead to mainly symptomatic complications when steroids are withdrawn. The slight decrease in glomerular filtration rate probably can be ascribed mostly to the effect of steroids on systemic renal haemodynamics. It is recommended to consider cessation of steroid medication within 48 months of therapy, and after determination of basal cortisol to identify patients with potential complications

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Original Article

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Abstract

Background. Withdrawal of steroids should be attempted after organ transplantation because of their adverse cardiovascular and metabolic effects. However, immunological, haemodynamic and symptomatic complications may occur due to the suppression of endogenous corticoid hormone synthesis under exogenous steroid intake. We have examined the effect of chronic steroid medication on adrenocortical function, and of steroid withdrawal, in immunologically stable renal transplant patients.

Methods. Sixty-three patients under long-term prednisone therapy (mean ± SD 36 ± 47 months) were assessed regarding basal fasting cortisol concentration and adrenocortical stimulation by the low-dose Synacten test both prior to and after stepwise prednisone withdrawal. Renal graft function (determined as the calculated glomerular filtration rate according to the Cockroft–Gault formula), mean arterial blood pressure and clinical status were evaluated concomitantly.

Results. Basal fasting cortisol concentration was clearly suppressed in 14% of patients under long-term steroid medication, and adrenocortical stimulation by the low-dose Synacten test was impaired in 31% after steroid withdrawal. About a third of all patients were symptomatic with fatigue (60%), arthralgias (60%), muscular weakness (20%), loss of appetite (20%), hypotension (15%) or headaches (5%). The incidence of symptoms was much higher in patients with low basal fasting cortisol concentration prior to steroid withdrawal, and after >2 years of steroid medication. Renal graft function, determined as glomerular filtration rate, decreased only slightly overall by ~5%, and was more pronounced in symptomatic *vs* asymptomatic patients (−7 *vs* −2 ml/min, respectively), as was the fall in mean arterial pressure (−10 *vs* −4.2 mmHg, respectively).

Conclusions. Adrenal function is impaired in renal transplant patients receiving long-term steroid medication as part of their immunosuppressive regimen. This may lead to mainly symptomatic complications when steroids are withdrawn. The slight decrease in glomerular filtration rate probably can be ascribed mostly to the effect of steroids on systemic renal haemodynamics. It is recommended to consider cessation of steroid medication within 48 months of therapy, and after determination of basal cortisol to identify patients with potential complications.

Keywords: adrenal glands; adrenocortical function; prednisone therapy; renal graft function; steroids; steroid withdrawal

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Introduction

Corticosteroids have been the cornerstone of immunosuppressive therapy in transplant medicine for decades. Even with the advent of newer, more specific and increasingly potent immunosuppressants, such as calcineurin inhibitors, mycophenolate or sirolimus, steroids have remained part of the initial immunosuppressive regimen after kidney transplantation in most centres. However, due to their untoward metabolic and cardiovascular effects, it is recommended to withdraw corticosteroids if the immunological situation of the patient allows for it [1]. Unfortunately, both short- and long-term glucocorticoid treatment in non-transplant patients has been reported to cause transient adrenocortical dysfunction due to suppression of the hypothalamo-adrenal axis by exogenous steroid administration [2–4]. Thus, cessation of long-term steroid medication may be difficult, not only from an immunlogical point of view with the risk of acute rejection episodes in transplant patients, but also due to impairment of adrenocortical function with symptomatic manifestations from steroid withdrawal (SW). In addition,

cessation of exogenous steroid intake may impact on the renal transplant independently of immunological mechanisms. Animal studies by Baylis Brenner *et al.* have shown corticosteroids to increase renal plasma flow and thus glomerular filtration rate (GFR) [5]. Based on this knowledge, one would expect cessation of long-term steroid administration to impair renal graft function acutely. Similarly, a decrease in systemic blood pressure has to be postulated because of the salt and water retention attributed to steroid hormones. However, no data are available from the literature on adrenocortical function in renal transplant patients under long-term steroid medication, and on the consequences of steroid withdrawal with regard to adrenocortical response and its relationship to changes in renal function, systemic blood pressure and the development of symptomatic complications. Therefore, it was the aim of this study to examine the effect of chronic steroid therapy on adrenocortical function, and of the withdrawal from long-term corticosteroid medication on graft function, arterial blood pressure and the potential development of symptomatic complications from adrenal insufficiency in immunologically stable renal transplant patients.

Materials and methods

A cohort of 63 solid organ transplant patients with SW between October 2001 and June 2003 were included prospectively in this single-centre study. Fifty-five kidney transplant patients were on cyclosporin A (CyA)/mycophenolate mofetil (MMF)-based immunosuppression, while eight patients with combined kidney and pancreas grafts were treated with tacrolimus and MMF. Recent publications have reported the feasibility of SW in the latter group of patients [6]. Most of the patients were recipients of a first graft, with only three having undergone repetitive transplantation. The baseline characteristics of all patients are listed in Table 1.

Table 1. Baseline characteristics of the study population

	All patients ($n = 63$)
Cadaveric/living donor, *n*	47/16
Transplanted organ	
Kidney (*n*)	55
Kidney and pancreas (*n*)	8
Age (years)	45.8 (12.2)
Male:female ratio	44:19
Number of Tx	
1	59
2	3
3	1
Time after last transplantation (months)	27 (36)
Time on steroids (months)	36 (47)
Serum creatinine (μmol/l)	122.2 (23.8)
GFR (ml/min)	65.3 (14.6)
MAP (mmHg)	101.9 (12.6)

All results are means; SDs are given in parentheses.
GFR = glomerular filtration rate; MAP = mean arterial blood pressure.

All patients were on medication with 10 mg of prednisone (PDN) per day at baseline for at least 6 months. SW was then carried out stepwise over 2 weeks by first tapering the PDN dose to 5 mg before complete withdrawal (Figure 1). Basal fasting cortisol (BFC) was assessed in all 63 patients at baseline and 1 week after SW between 8 and 9 a.m. The normal range of BFC as defined for the employed assay is 171–536 nmol/l. Plasma cortisol was measured by ECLIA (Roche Diagnostics®, Mannheim, Germany), with a coefficient of variation of 2.9%. This assay does not interfere with exogenously administered synthetic steroids or their metabolites, and, therefore, exclusively detects endogenous corticosteroid hormones. In a subgroup of 32 patients, adrenal function was examined by low-dose Synacten® (tetracosactide, Novartis Pharma, Switzerland) stimulation (LDS; intravenous bolus injection of 1 μg tetracosactide) at baseline and after SW. The commercially available 250 μg vials of Synacten® were diluted by the hospital pharmacy to 1 μg/ml in chemically inert plastic tubes and stored at 4°C until use within 24 h. The LDS test is established and widely validated with a high specificity and sensitivity both for detection of primary hypoadrenalism and the assessment of adrenocortical function in patients under exogenous steroid medication [7–10]. In accordance with other authors, a plasma cortisol concentration of >550 nmol/l after 30 min of Synacten® injection had been defined as being indicative for adequate adrenal response [4].

Clinical evaluation and data collection were performed at baseline, 1 week after steroid tapering to 5 mg, and finally 1 week after completion of SW. Longer follow-up beyond 3 months after the final predefined time point was available for most patients. Patients were interviewed and examined with particular emphasis on typical symptoms of SW-like fatigue, malaise, loss of appetite, headache as well as muscle and joint pain. All patients were negative regarding these symptoms and in a stable general condition prior to initiation of steroid tapering. Furthermore, renal function was assessed by serum creatinine (SCr) and calculated GFR according to the Cockroft–Gault formula. Changes in systemic arterial blood pressure throughout SW were determined in a sitting position on the upper extremities. For the purpose of comparison between groups, mean arterial pressure (MAP) was used.

For data analysis, patients were divided into subgroups according to BFC concentration prior to SW (group A, BFC <171 nmol/l; group B, BFC >170 nmol/l). The two groups were then compared regarding renal function, MAP and clinical symptoms. Similarly, results were analysed independently of the presence or absence of symptoms related to SW. Finally, the subgroup of patients subjected to the LDS test was divided further and analysed according to their adrenocortical response upon stimulation after PDN therapy had been stopped [group C, stimulated plasma cortisol (CST)

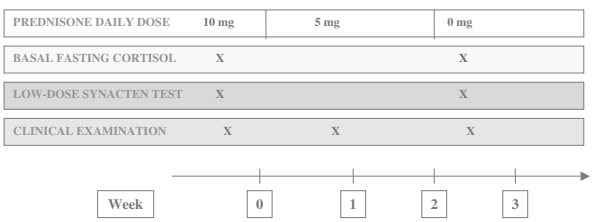

Fig. 1. Schedule of steroid withdrawal.

concentration <550 nmol/l; group D, plasma CST concentration >550 nmol/l].

All patients participating in the study have given written informed consent. The study protocol was performed according the guidelines of the institutional ethics committee.

All results are expressed as means and SD unless stated otherwise. Differences between groups were analysed by paired or unpaired Student's *t*-test, as appropriate, with a *P*-value <0.05 indicating statistical significance.

Results

The effects of SW as analysed in all patients are summarized in Table 2. The mean BFC concentration before and after SW was within the normal range, but slightly lower after SW compared with baseline by ~20%. SCr increased from 122 µmol/l at baseline to 130 µmol/l 1 week after SW ($P = 0.0001$), corresponding to a drop in GFR of ~5% from 65 to 62 ml/min. MAP decreased significantly after SW from 102 to 96 mmHg ($P = 0.0002$). Whereas none of the patients were reporting any particular symptoms prior to initiation of steroid tapering, 20 patients (32%) developed one or more symptoms typically related to SW after medication had been stopped completely. In their order of frequency, the most commonly cited were fatigue (60%), arthralgias (60%), muscular weakness (20%), loss of appetite (20%), hypotension (15%) or headaches (5%). The occurrence of symptoms and/or worsening of renal transplant function necessitated the reinstitution of steroid medication in seven patients. The reasons and outcomes are listed in Table 3. As shown, another attempt to withdraw steroids later on was successful in one of these seven patients, and PDN dose could be reduced to 5 mg/day in two other patients.

A minority of nine patients (14%) had inadequately low BFC levels prior to cessation of steroid therapy (group A), defined as a BFC of <171 nmol/l. Mean BFC

Table 2. Characteristics of all transplant patients subjected to steroid withdrawal and randomization according to baseline basal fasting cortisol

	All patients		Group A (BFC <171 nmol/l)		Group B (BFC >170 nmol/l)	
n (%)	63 (100)		9 (14)		54 (86)	
Age (years)	45.8 (12.2)		39.3 (7.9)*		46.9 (12.5)	
Gender ratio, M:F	44:19		5:4		39:15	
Time on steroids (months)	36 (47)		34.0 (45.3)		46.8 (59.9)	
	Baseline	After SW	Baseline	After SW	Baseline	After SW
BFC (nmol/l)	459 (205)	376 (122)$^{+}$	71 (52)†	311 (96)	523 (137)	387 (124)
SCr (µmol/l)	122 (23.8)	130 (28.3)$^{+}$	116 (24.1)	125 (21.3)	123 (23.8)	131 (29.4)
GFR (ml/min)	65 (14.6)	62 (14.4)	68 (13.4)	63 (15.0)	65 (14.9)	62 (14.5)
MAP (mmHg)	102 (12.6)	96 (12.1)$^{+}$	100 (8.5)	97 (7.4)	102 (13.2)	96 (12.7)
Change in GFR (ml/min)	−3.6 (7.3)		−4.9 (8.0)		−3.3 (7.3)	
Change in MAP (mmHg)	−6.1 (12.6)		−3.1 (5.4)		−6.6 (13.4)	
Symptoms of SW *n* (%)	20 (32)		9 (100)		11 (20)	

All results are means; SDs are given in parentheses.
BFC = basal fasting cortisol; SCr = serum creatinine; GFR = glomerular filtration rate; MAP = mean arterial blood pressure; SW = steroid withdrawal.
*$P = 0.04$ *vs* group B; $^{+}P < 0.001$ *vs* baseline in all patients; $^{\dagger}P < 0.0001$ *vs* baseline in group B.

Table 3. Reinstitution of steroid medication in seven of 63 patients after steroid withdrawal

Patient	TOS (months)	BFC (nmol/l)	Reason for reinstitution	Days after SW	Follow-up/outcome
G.R., 44-year-old male	8	516	Rise in serum creatinine because of post-renal obstruction	30	Surgical intervention with normalization of serum creatinine; PDN discontinued
B.P., 66-year-old male	63	344	Hypotension, loss of appetite, fatigue	16	Prompt recovery under continued low-dose steroid medication (5 mg/day)
R.A., 27-year-old male	8	482	Asymptomatic rise in serum creatinine	70	Creatinine normalized, steroids continued (10 mg/day)
M.E., 49-year-old female	100	451	Fatigue, rise in serum creatinine due to pre-renal complication (acute diarrhoea)	9	Complete recovery; low-dose steroids continued (5 mg/day)
L.S., 45-year-old male	163	573	Fatigue, joint pain, loss of appetite, rise in serum creatinine	29	Complete recovery, steroids continued (10 mg/day)
C.C., 58-year-old male	127	572	Joint pain	16	Recovered; steroids continued (10 mg/day)
S.I., 70-year-old female	15	695	Fatigue, joint pain, loss of appetite, rise in serum creatinine	7	Recovered; steroids continued (10 mg/day)

TOS = time on steroids prior to withdrawal; BFC = basal fasting cortisol prior to steroid withdrawal; SW = steroid withdrawal.

Table 4. Patients with symptomatic compared with patients with asymptomatic steroid withdrawal

	Symptomatic		Asymptomatic	
$n = 63$ (100%)	20 (32)		43 (68)	
Age (years)	45.5 (11.3)		46.0 (12.5)	
Gender ratio M:F	13:7		31:12	
	Baseline	After SW	Baseline	After SW
BFC (nmol/l)	287 (222)	326 (121)$^{+}$	539 (137)$^{+}$	400 (117)
CST (nmol/l)*	503 (198)	573 (109)	653 (125)	632 (126)
Increased cortisol (nmol/l)*	153 (150)	227 (55)	86 (89)	220 (122)
SCr (μmol/l)	123 (23.3)	140 (35.8)$^{+}$	122 (24.1)	126 (26.3)
GFR (ml/min)	64.5 (16.9)	57.5 (16.4)	65.7 (15.2)	63.8 (14.3)
MAP (mmHg)	102 (9.2)	92 (10.7)	101 (14.1)	98 (12.3)†
Change in GFR (ml/min)	−7.0 (8.1)		−2.0 (6.4)†	
Change in MAP (mmHg)	−10.0 (12.3)		−4.2 (12.4)†	
Time on steroids (months)	58 (53)		25 (40)‡	

All results are means; SDs are given in parentheses.
BFC = basal fasting cortisol; CST = stimulated cortisol; SCr = serum creatinine; GFR = glomerular filtration rate; MAP = mean arterial blood pressure; SW = steroid withdrawal.
*$n = 32$.
$^{+}P < 0.001$ *vs* baseline in symptomatic patients; $^{\dagger}P < 0.05$ *vs* in symptomatic patients after SW; $^{\ddagger}P = 0.004$ *vs* in symptomatic patients.

at baseline in group A was lower by ~8-fold compared with patients with normal BFC (group B). Patients of group A were slightly younger, and low BFC concentration was clearly associated with the occurrence of clinical symptoms related to SW (with a prevalence of 100% in group A, *vs* 20% in group B). However, no significant differences between groups were noticed regarding renal function, blood pressure and time on steroids. It is of note that the difference in mean BFC concentration after SW was clearly less between groups, indicating that in some of the patients from group A cortisol production was about to be restored.

Comparing symptomatic with asymptomatic patients after SW, some important differences could be detected (Table 4). As a reflection of the findings reported in Table 2, BFC prior to SW was significantly higher in asymptomatic compared with symptomatic patients by ~2-fold. The individual correlation of BFC prior to and after cessation of steroids in patients with and without symptoms is shown in Figure 2. In addition to low BFC, renal function was significantly worse in symptomatic *vs* asymptomatic patients, as revealed by the differences in SCr and GFR. Also, blood pressure was significantly lower in symptomatic patients after SW compared with patients without symptoms, with a mean decrease in MAP of 10.0 and 4.2 mmHg, respectively. Finally, symptomatic patients had been

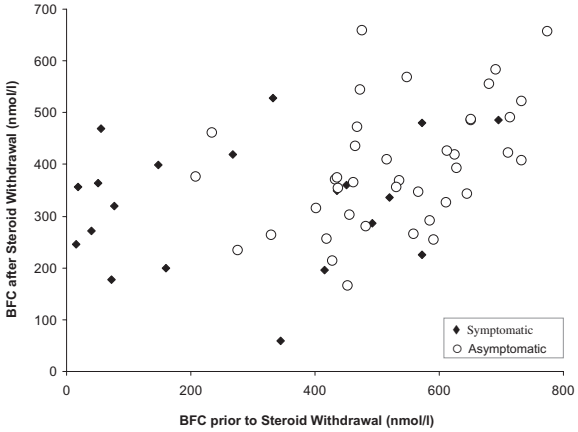

Fig. 2. Correlation of basal fasting cortisol (BFC) prior to and after steroid withdrawal in symptomatic and asymptomatic patients.

on steroids significantly longer than patients without symptoms from SW.

The subgroup of patients tested for adrenal response by LDS ($n = 32$; Table 5) was comparable with the entire cohort (Table 2) regarding the baseline characteristics such as age, gender, duration of steroid medication, BFC, GFR and MAP. Ten of these patients (31%) presented with an impaired adrenal response to LDS (group C), defined as a plasma CST concentration below 550 nmol/l at the start of SW. Compared with the 22 patients (69%) with normal adrenocortical response (group D), their CST concentration 1 week after SW was ~35% lower. Impaired adrenal response after SW was associated with both longer time on steroid medication (by ~2-fold) and higher incidence of symptoms related to SW (by ~55%). In contrast, no significant differences were found with respect to patient age, changes in SCr, GFR and MAP (Table 5).

Discussion

Due to its untoward metabolic effects on bone, carbohydrate metabolism and the cardiovascular system, it is desirable to withdraw corticosteroid medication after kidney transplantation in immunologically stable patients. Many studies have investigated the feasibility of steroid-free immunosuppression regarding long-term graft survival. However, to the best of our knowledge, this is the first study that reports on the short-term effects of SW with respect to haemodynamic stability, graft function and clinical symptoms of SW in renal transplant patients. The main findings of our experiments are that (i) a substantial proportion of patients on long-term corticosteroid treatment have a suppressed adrenocortical function with inadequate response of the adrenal glands upon stimulation; (ii) nevertheless, SW can be performed safely in the vast majority of chronically stable renal transplant patients with regard to preservation of graft function; and (iii) the limiting factor for successful SW is the development of symptoms such as musculoskeletal

Table 5. Characteristics of patients subjected to steroid withdrawal assessed by low-dose ACTH adrenal stimulation test (LDS), and comparison of subgroups according to adrenal response upon LDS

	All patients		Group C (CST <550 nmol/l)		Group D (CST >549 nmol/l)	
n (%)	32 (100)		10 (31)		22 (69)	
Age (years)	48.6 (11.4)		43.9 (6.7)		49 (12.6)	
Gender ratio M:F	24:8		9:1		15:7	
Time on steroids (months)	49.1 (56.3)		91.8 (84.5)*		42.6 (54.1)	
	Baseline	After SW	Baseline	After SW	Baseline	After SW
BFC (nmol/l)	483 (188)	383 (120)	399 (207)	261 (58)†	514 (176)	441 (94)
CST (nmol/l)	592 (165)	595 (135)	466 (164)‡	432 (67)†	643 (139)	669 (82)
Δ cortisol CST–BFC (nmol/l)	111 (117)	223 (101)	60 (81)	171 (103)	129 (124)	227 (116)
Δ cortisol CST–BFC (%)	55 (98)	67 (37)	67 (124)	74 (47)	51 (89)	57 (36)
SC (μmol/l)	130 (25.2)	138 (31.7)+	130 (21.0)	135 (27.8)	127 (27.3)	138 (33.8)
GFR (ml/min)	62 (14.4)	58 (13.0)+	67 (20.3)	64 (18.3)	63 (14.1)	58 (12.8)
MAP (mmHg)	100 (11.2)	97 (12.9)	105 (10.2)	98 (10.1)	100 (12.1)	97 (13.8)
Change in GFR (ml/min)	−3.9 (6.1)		−2.6 (5.7)		−4.8 (6.3)	
Change in MAP (mmHg)	−3.6 (12.7)		−7.2 (10.6)		−2.9 (13.5)	
Symptoms of SW, *n* (%)	12 of 32 (38)		5 of 10 (50)		7 of 22 (32)	

All results are means; SDs are given in parentheses.
BFC = basal fasting cortisol; CST = stimulated cortisol; SCr = serum creatinine; GFR = glomerular filtration rate; MAP = mean arterial pressure; SW = steroid withdrawal.
*$P = 0.028$ *vs* mean time on steroids in group D; +$P < 0.01$ *vs* mean baseline in all patients; †$P < 0.0001$ *vs* group D after SW; ‡$P = 0.002$ *vs* group D at baseline.

pain, fatigue and hypotension, which can be predicted by basal plasma cortisol concentration prior to cessation of corticosteroid therapy.

Among our cohort of chronically stable renal transplant patients, who have been on corticosteroid treatment for an average of 3 years, about a third had an impaired adrenocortical function, with either low BFC concentration (< 171 nmol/l) in 14% or inadequate adrenocortical response upon stimulation with a synthetic derivative of adrenocorticotrophic hormone (ACTH; tetracosactide, Synacten®) in 32% of subjects. One may argue that steroid tapering in our study was faster compared with current practice, and may account for the findings reported above. Nevertheless, the incidence of adrenal insufficiency in our cohort is lower compared with results from studies in non-transplant patients after both long-term and short-term glucocorticoid therapy, which revealed an impaired adrenocortical response in 63 [2] and 45% [4] of patients, respectively. One may speculate on whether transplant patients behave differently from patients who receive steroid medication for other reasons, i.e. inflammatory or autoimmune disease. One such potential difference may be the concurrent therapy with other immunosuppressive drugs in transplant patients that can interfere with the action and/or the metabolism of corticosteroids, as described for CyA [11,12]. However, the average CyA dose used in our study was not different between patients with and without impaired adrenocortical response (data not shown). Alternatively, the regulation of adrenal tissue, that variably is transplanted with a renal graft, may be regulated differently from that of 'native' kidneys.

With regard to the implications of the observed impairment in adrenocortical function in renal transplant patients under long-term steroid medication, one has to differentiate direct effects on the graft from other consequences. It is reassuring to notice that SW had almost no impact on graft function in this study, at least in short-term follow-up. Although the mean GFR was reduced by ∼4 ml/min immediately after SW, corresponding to a decrease in renal transplant function of <6%, only a few patients were suspected to have a rejection episode. Consequently, GFR stabilized in virtually all patients either spontaneously or after reintroduction of steroid medication during several weeks of follow-up, and no patient required anti-rejection therapy. Although many other studies have demonstrated that SW is possible in a majority of patients without relevant rejection episodes (for a review see [13]), the particularly favourable outcome in our patient cohort may be explained mainly by two facts: all patients were under an immunosuppressive regimen based on CyA and MMF, and were selected for SW only when they had a previously stable graft function. The slight and transient decrease in GFR that nevertheless occurred is in accordance with the effect of corticosteroids on renal haemodynamics and the regulation of intraglomerular pressure [5]. As corticosteroids can increase intraglomerular filtration pressure and, thereby, GFR, it is conceivable that SW may have the opposite effect. Thus, many of the renal transplant patients undergoing cessation of long-term steroid medication with consecutive deterioration of renal graft function may not necessarily experience a rejection episode, and, therefore, reintroduction of steroid therapy may be unnecessary. In the present study, there was a trend towards a more pronounced drop in GFR in patients with low BFC (Table 2), and in those with symptoms after SW. These findings are in accordance with the aforementioned hypothesis. However, no such correlation was found

with the adrenal response upon the low-dose ACTH stimulation test (Table 5). The occurrence of symptoms and arterial hypotension may be the more sensitive 'markers' for the susceptibility to worsening of renal graft function from SW than the adrenocortical response assessed by ACTH stimulation test. Nevertheless, no definite conclusion can be drawn regarding the cause and effect relationship between SW and changes in renal graft function due to intraglomerular pressure mechanisms.

A more clear-cut picture can be drawn from the present results with respect to the interdependence of symptoms related to the cessation of steroid medication and adrenocortical response in renal transplant patients. About a third of all patients in this study developed manifestations related to SW, such as fatigue, arthralgias, muscular weakness, loss of appetite, hypotension or headaches (Table 2). This percentage was even higher in patients with an inadequate LDS test (Table 5), and rose to 100% in those with low BFC concentration prior to cessation of steroid medication. The latter is in accordance with findings in non-transplant patients undergoing long-term corticosteroid therapy [14]. Moreover, a similar pattern was revealed for changes in MAP. As expected, MAP dropped by ~6 mmHg when all patients were analysed together. In fact, arterial hypertension, or poorly controlled arterial blood pressure, are among the most relevant complications of chronic steroid therapy. Therefore, lowering of MAP is a beneficial effect of SW. However, the decrease in blood pressure was more pronounced in patients with low BFC (Table 2) and/or inadequate CST concentration after ACTH administration (CST <550 nmol/l; Table 5). As the occurrence of symptoms from SW matches well with these groups of patients, it is conceivable that at least part of the manifestations, such as fatigue and headache, are conferred by changes in blood pressure. Finally, our study has revealed time on steroid medication to be the most relevant determinant for the occurrence of symptoms from cessation of steroids in renal transplant patients. A note of caution may be warranted with regard to the steroid tapering scheme used in our trial. Except for study conditions with frequent and careful monitoring of the patients undergoing SW, a more prolonged course of stepwise dose reduction may be advisable.

What are the practical implications from our findings? Our data indicate that renal transplant patients on long-term corticosteroid therapy are comparable in general regarding adrenocortical function with patients receiving steroids for other indications. Thus, similar complications can be anticipated when therapy is stopped, and the same precautions should be taken, especially in patients after many years on treatment. Surprisingly, cessation of steroid medication almost exclusively failed because of symptomatic manifestations, and not due to graft failure. However, reinstitution and continuation of steroids was necessary only in six patients (Table 3). As SW seems clearly less likely to result in complications when performed within the first 2 years of therapy, it is recommended to stop medication within this period. Measuring BFC prior to cessation of therapy is helpful, as low levels can identify patients susceptible to develop symptoms after SW. With regard to the renal graft, it should be kept in mind that worsening kidney function after cessation of steroids may not always indicate rejection, but is probably more likely to be due to systemic and renal haemodynamic effects of corticosteroid hormones. Thus, prior to resumption of long-term steroid therapy, this possibility should be considered, and a graft biopsy performed to avoid unnecessary treatment.

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Conflict of interest statement. None declared.

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